attached hereto, by deleting the bracketed matter and inserting the underlined matter. A clean copy of claims 1, 2, 6-8 and 12, as amended, is attached as Exhibit B.

**REMARKS**

Claims 1-12 are pending and presented for examination in the subject application.

Applicants have herein amended claims 1, 2, 6-8 and 12 to point out more clearly and distinctly the subject matter applicants regard as the invention. It is submitted that the claim amendments do not introduce new matter and do not change the scope of the claimed invention. Accordingly, applicants respectfully request entry of this Amendment.

**Rejection under 35 U.S.C. § 112, second paragraph**

In Section 6 of the December 14, 2000 Office Action, claims 1 and 7 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for purportedly failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

The Examiner stated that claims 1 and 7 are allegedly indefinite for reciting the term "known structural information and functional information", as the skilled artisan purportedly would not be able to determine the metes and bounds of this limitation.

The Examiner also stated that claims 1 and 7 are allegedly indefinite for reciting the phrase "corresponding homologous sequence information", as it is purportedly not clear which sequences would be determined to have "corresponding homology" and the sequences that do not, as would be reasonable for

establishing the families.

The Examiner also stated that claims 1 and 7 are allegedly indefinite for reciting the phrase "appropriately representative", as purportedly neither the claims nor specification define which members are appropriately representative, and those members of the family that are not appropriately representative.

The Examiner also stated that claims 1, 2, 7 and 8 are allegedly indefinite for using the generic pronoun "ones" to refer to a previously established limitation. The Examiner stated that an amendment replacing the term "ones" with the specific limitation which already has proper antecedent basis would overcome this rejection.

The Examiner also stated that claims 1 and 7 are allegedly indefinite for reciting the phrase "...that are effective as proteins", as it is purportedly not clear with respect to the manner in which a synthesized protein would not be an "effective" protein.

The Examiner also stated that claims 1 and 7 are allegedly indefinite for reciting the phrases "predetermined diffraction characteristics" and "suitable" in determining which crystal are of reasonable quality for x-ray diffraction measurements as the skilled artisan purportedly would not reasonably be able to determine the metes and bounds of these limitations. The Examiner further stated that page 16 of the instant specification speaks to the general steps of preparing crystals, but there is purportedly no guidance for the suitable determination step.

The Examiner also stated that claims 1 and 7 recite the limitation "other known three-dimensional structures", and there is purportedly insufficient antecedent basis for this limitation in the claim. The Examiner further stated that this phrase assumes that a three-dimensional structure has already been established for the target. The Examiner stated that applicants purportedly have not clearly set forth in the method the point where the three-dimensional structure has become "known" or determined.

The Examiner also stated that claims 1 and 7 are allegedly indefinite for reciting the limitation "known" in reference to the known three-dimensional structure stored in the databases, as it is purportedly not clear how this factor is "known". The Examiner further stated that an amendment deleting the term "known" would overcome this rejection.

The Examiner also stated that claims 1 and 7 are allegedly indefinite for reciting the phrase "homology model", as the skilled artisan purportedly could not reasonably be able to determine the metes and bounds of the model (i.e., what the essential parameters are, and their relationships to one another).

The Examiner also stated that claims 1 and 7 are allegedly indefinite for reciting the phrase "along with" as a means to describe a step carried out with a bioinformatics tool and the developed homology model. The Examiner further stated that an amendment replacing the phrase "along with" using the term "and" would overcome this rejection.

The Examiner also stated that claim 7 is allegedly indefinite for

purportedly failing to recite a final process step which agrees back with the preamble. The Examiner further stated that while minor details are not required in method/process claims, at least the basic steps must be recited in a positive, active fashion. The Examiner stated that claim 7 is drawn to a method of determining experimentally a plurality of three-dimensional atomic structures, while the claim recites a final step of developing a homology model using computational tools.

The Examiner also stated that claims 6 and 12 are allegedly indefinite for reciting the phrase "more appropriate constructs", as the skilled artisan purportedly would not have reasonable guidance in determining this limitation.

In response, without conceding the correctness of the Examiner's position but solely to advance the prosecution of the subject application, applicants have hereinabove amended claims 1, 2, 6-8 and 12 to clarify the claim language. It is submitted that the claim amendments do not change the scope of the claimed invention.

With regard to the phrase "corresponding homologous sequences", applicants respectfully refer the Examiner to the specification at, for example, page 14, lines 5-9 and 18-23. Applicants maintain that claims 1 and 7 would be clear and unambiguous to one of ordinary skill in the art with knowledge of the term "homologous sequence" as used in the art and further guided by the claims and the specification.

With regard to the terms "predetermined diffraction characteristics" and "suitable specimen crystals", applicants respectfully refer the Examiner to the specification at, for

example, page 6, lines 18-28, page 18, lines 25-28. In addition, the specification lists at pages 24-26 several published papers authored/co-authored by the applicants, including Hendrickson et al., The EMBO Journal 9, 1665-1672, 1990 (hereinafter "Hendrickson paper"), which describe the state of the art. Suitable diffraction characteristics of the crystals is described at, for example, page 1667 (and shown in Figure 3) of the Hendrickson paper. Applicants maintain that claims 1 and 7, as amended, would be clear and unambiguous to one of ordinary skill in the art with knowledge of the state of the X-ray crystallography art and further guided by the claims and the specification.

With regard to the phrase "homology model", applicants respectfully refer the Examiner to the specification at, for example, page 6, lines 7-16, and page 20 line 35 through page 21, line 6. Applicants maintain that claims 1 and 7, as amended, would be clear and unambiguous to one of ordinary skill in the art with knowledge of the term "homology model" as used in the art and further guided by the claims and the specification.

With regard to the phrase "constructs for experimental analysis", applicants respectfully refer the Examiner to the specification at, for example, page 3, lines 4-13, and page 21, lines 10-20. Applicants maintain that claims 6 and 12, as amended, would be clear and unambiguous to one of ordinary skill in the art as guided by the claims and the specification.

Applicants respectfully submit that step (i) ["developing a homology model ..."] is not inconsistent with the preamble of claim 7, and does not render claim 7 indefinite. As applicants pointed out in the specification at, for example, page 21, lines

9-20, homology models may be used in the experimental determination process, such as during target selection. Thus, step (i) is consistent with claim 7 as a whole, as well as with the purpose set forth in the preamble.

Applicants respectfully submit that amended claims 1, 2, 6-8 and 12 clearly recite the subject matter applicants regard to be the invention. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 112, second paragraph.

**Rejection Under 35 U.S.C. § 103(a)**

In Section 9 of the December 14, 2000 Office Action, claims 1, 3, 5-7, 9, 11 and 12 were rejected under 35 U.S.C. § 103(a) as purportedly being unpatentable over Bachar et al., Protein Engineering 6, 279-288, 1993 (hereinafter "Bachar paper"), in view of the Hendrickson paper, in view of Everett et al., Nature Genetics 17, 411-422, 1997 (hereinafter "Everett paper"), and in view of Andrea et al., J. Med. Chem. 34, 2824-2836, 1991 (hereinafter "Andrea paper").

The Examiner stated that claims 1, 3, 5-7, 9, 11 and 12 are drawn to a system and process for determining experimentally a plurality of three-dimensional atomic structures, each associated with a corresponding protein, first a protein database of sequence information and known structural and functional information, which is systematically organized, purportedly must be established for integration with at least one bioinformatics tool using the structural and functional information to cluster the plurality of proteins into a plurality of families, in which members of each family have corresponding homologous sequences. The Examiner also stated that, afterwards, the analysis of the

target protein using the sequence information corresponding to other family members of the database and information corresponding to other known three-dimensional structures which is stored in the database, with means for refining the model for functional motifs, and means for defining at least one class of compound predicted to have binding potency using the active site information.

The Examiner stated that the Bachar paper teaches a method/system for protein classification, wherein an experimentally-derived, three-dimensional structure of a target protein can be classified by assignment to a cluster set of structurally similar, three-dimensional representation of proteins in an organized database. The Examiner stated that the design and organization of the database consists of three major steps: 1) finding relatively small subsets of the structures that form an initial match; 2) finding clusters of initial matches that represent similar transformations; and 3) extending the clusters to contain additional matching pair residues. The Examiner also stated that these steps are further comprised of sub-steps detailed in the disclosure. The Examiner stated that as a result of organizing a database and developing a means to utilize the database for similarity comparisons/clustering, one can determine a surface motif in a target protein, one can determine an activity of a given compound to the target protein, and one can objectively determine a number of chemical or biological properties of the target protein, such as active sites, surface properties, cores, etc.

The Examiner acknowledged that although the Bachar paper describes utilizing data which represent the three-dimensional structures of proteins, the Bachar paper does not disclose a

means for preparing proteins, a means of preparing protein crystal for analysis, a means of three-dimensional analysis, or any peripheral mean for data acquisition. The Examiner also acknowledged that the Bachar paper does not specifically teach the use of sequence information for classification, or compound classification to the clustered proteins.

The Examiner stated that the Hendrickson paper teaches a system and process for incorporating selenomethionine (as a replacement for methionine) into recombinant proteins produced from plasmids in E. coli, which are crystallized and analyzed by multiwavelength anomalous diffraction (MAD) as a means for producing a three-dimensional representation of a target protein. The Examiner also stated that the method described in the Hendrickson paper provides the advantages over conventional X-ray techniques for elucidating three-dimensional protein structures, in that MAD utilizes the scattering effects of resonance between X-rays and bound atomic orbitals, it is perfectly isomorphic, allows for data sampling from a single crystal, and the analysis is algebraically exact.

The Examiner stated that the Everett paper discloses a method/system for characterizing/clustering proteins into families based on their sequence and structure, such as using their linear sequence and by characterizing transmembrane regions using PHDhtm. The Examiner also stated that a function is then assigned to an unknown protein based on a similarity comparison of the target protein to the proteins which have been clustered into families which also have functional information. For example, a function of sulfate transport is assigned to pendrin based on the family clustering model which classified pendrin in the family of other sulfate transporters, and the observed

physiological effects that are present which correlate with sulfate transport deficiency in those diagnosed with Pendred syndrome. The Examiner further stated that the Everett paper discloses that these bioinformatics tools are advantageous in that they reduce experimental efforts of trial and error, wherein researchers would otherwise be uncertain of the target protein's function.

The Examiner stated that the Andrea paper discloses a method/system for clustering objects in multi-dimensional space as a means of characterizing the binding relationships between proteins and chemical compounds in a database through quantitative structure-activity relationships (QSARs).

The Examiner alleged that it would have been purportedly obvious to one of ordinary skill in the art at the time the invention was made to utilize sequence and structure data as taught by the Everett paper, with the method of the Bachar paper as a means to more selectively determine proteins of interest based on a given or suspected function, before utilizing the protein structural determination means as taught by the Hendrickson paper (i.e., selenomethionyl protein expression technique for MAD analysis because of the aforementioned advantages of using their method/system for recovering data sets representing the three-dimensional structure of proteins over conventional x-ray crystallographic methods). The Examiner stated that the Bachar paper purportedly discloses that although sequence-based classification schemes are not flawless, these methods can prove to be quite useful in protein family classification, and would be improved upon if applied to the sequence-independent method for three-dimensional structural refinement. The Examiner further alleged that one would recognize that the refined model

and structure of the experimentally examined protein would provide an improved and refined overall model, and the physicochemical features of the refined target protein whose structure has been determined could be applied to the other protein family members which were originally classified based on sequence information. The Examiner alleged that one of ordinary skill in the art purportedly would be motivated to implement the QSARs methodology as disclosed by the Andrea paper, as a means to determine which chemical structure (or family of chemical structures) associate with a given protein structure (or family thereof). The Examiner alleged that, therefore, the invention as a whole purportedly would have been prima facie obvious at the time the invention was made.

Applicants maintain that the Bachar paper, the Hendrickson paper, the Everett paper and the Andrea paper do not render unpatentable the invention set forth in claims 1, 3, 5-7, 9, 11 and 12. The claimed invention is patentable over the Bachar paper, the Hendrickson paper, the Everett paper and the Andrea paper for at least the following reasons.

The subject application provides a novel and unobvious method and system for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein having an upto-then unknown structure. Sequence information for a plurality of proteins and structural information and functional information for selected proteins are systematically organized into a database. The sequence information, structural information and functional information stored in the database are used with a bioinformatics tool to cluster the plurality of proteins into families. In each such family, the members have homologous sequences. For each family,

a plurality of members of the family are selected as target proteins. The target proteins are synthesized. Synthesized products are screened, processed and crystallized into specimen crystals. The specimen crystals are tested for predetermined diffraction characteristics to determine suitable specimen crystals. High-throughput X-ray crystallography is performed on the suitable specimen crystals. Diffraction data obtained from the X-ray crystallography is analyzed and used to build and refine an atomic model of the corresponding target protein. The refined model of the target protein is analyzed using sequence information corresponding to other family members and structural information corresponding to other proteins, which are stored in the database, to determine functional motifs and surface characteristics to define active sites and macromolecular contact sites. The refined model also is used to develop a homology model of one or more predicted protein structures which in turn is used to develop further the database. The method and system may be used to develop a comprehensive structural genomics database.

The Bachar paper, which is the primary reference cited in the December 14, 2000 Office Action, relates to a method of comparing known protein structures in a sequence-independent manner. In the method described in the Bachar paper, regions of structural similarity between the structures are determined using three-dimensional (3-D) coordinate data of the known structures to be compared. The method described by the Bachar paper consists of the following major steps: (1) finding relatively small subsets of the 3-D structures that form an initial match; (2) finding clusters of initial matches that represent similar transformations; and 3) extending the clusters to contain additional matching pair residues.

The Bachar paper appears to describe a database of known 3-D protein structures. The Bachar paper does not describe or suggest, however, a system or method for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, as provided by the present invention. The Bachar paper fails to describe or suggest, for example, a basis for systematically organizing sequence information, structure information and functional information into a database in order to facilitate determination of protein structures for which structural information is not available in the database.

In order to cover the genomics space, the present invention provides for systematically organizing the already available information, including in particular the wealth of sequence information, for the proteins into a database, and using the information with a bioinformatics tool to cluster proteins into families, in which members of a family have homologous sequences. Using the information in the systematically organized database, a plurality of target proteins may be identified and synthesized for experimental structure determination via high-throughput X-ray crystallography. Diffraction data obtained through the X-ray crystallography are used to determine and refine 3-D atomic models of the target proteins. Bachar paper simply does not disclose or suggest such a novel and unobvious invention.

Further, the Bachar paper emphasizes that it teaches a **sequence-independent**, "pure" 3-D approach. For example, the Bachar paper states in the section entitled "Discussion" on page 286, in relevant part as follows:

> "... To date, all known methods search for geometric similarities between two proteins where a strict constraint has been placed in the search: sequential order

> conservation. ...
>
> ... applying such a constraint may be inadequate if the exact evolutionary relationship between the structures is unknown or when possible genetic mutations could have occurred (e.g. an interchange of segments in the sequence). **Structural comparison using such a constraint introduces a sequence-order bias into the results** as it assumes that the structures are evolutionarily related. In addition, sequence-independent structural comparison can help find common three-dimensional folding units (either with or without functional relationship). Thus, **it is important to be able to compare proteins in an unbiased, sequence-independent way**, especially if one is dealing with the question of convergence to a similar structure or divergence from a common ancestor. ..."

The Bachar paper further states in the section entitled "Conclusions" on page 286, in relevant part as follows:

> "... previous methods are at least partially constrained to linear matches, whereas the 'pure' 3-D approach of our method provides a way to obtain **sequence independent matches** not constrained by the 'progression rule' followed by current alignment techniques. ...
>
> Comparison of protein structures **in a sequence-independent method** provides a way of comparing distantly related and globally dissimilar proteins **without the bias introduced by previous methods of linear** protein structural alignment. Such linear global alignments are sometimes incomplete and inaccurate, whereas our method is capable of discovering partial structural similarities. ...
>
> ... Allowing superpositioning of structural units **independent of their sequential order** enables searches and detection of substructural motifs in the interior of protein molecules."

In view of, for example, the above-quoted portions of the Bachar Paper (see also the title of the Bachar paper), the Bachar Paper clearly teaches a sequence-independent approach to comparison of protein structures.

Moreover, the Bachar paper fails to describe or suggest, and indeed teaches away from, a system for determining experimentally

a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, which comprises at least the following: (i) a database of **sequence information** for a plurality of proteins, and structural information and functional information for selected proteins; (ii) at least one bioinformatics tool adapted to use **the sequence information**, structural information and functional information stored in the database to cluster the plurality of proteins into a plurality of families, in which, for each family, members of the family have corresponding **homologous sequences**; and (iii) structure extraction means having means for analyzing the refined model of the target protein **using sequence information** corresponding to other family members which is stored in the database and structural information corresponding to other proteins which is stored in the database, as set forth in thrice-amended claim 1.

Similarly, the Bachar paper fails to describe or suggest, and teaches away from, a process for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, which comprises at least the following steps: (a) **systematically organizing sequence information** for a plurality of proteins, and structural information and functional information for selected proteins into a database, (b) clustering the plurality of proteins into a plurality of families, in which, for each family, members of the family have corresponding **homologous sequences**, using at least one bioinformatics tool and **the sequence information**, structural information and functional information stored in the database, and (h) analyzing the refined model, stored in the database, of the target protein **using sequence information** corresponding to other family members which is stored in the database and structural information corresponding to other proteins which is

stored in the database, as set forth in thrice-amended claim 7.

Since the Bachar paper teaches away from these features, one skilled in the art would not have had motivation at the time of the present invention to combine the teachings of the Bachar paper with, for example, teachings of use of sequence data in the Everett paper. One skilled in the art would not have been motivated to combine the teachings of the Bachar paper with any teachings of these features in the prior art, without the present invention as a roadmap.

Therefore, it is submitted that the Bachar paper, considered alone or along with other references, would not have rendered the invention set forth in claims 1 and 7 obvious to one of ordinary skill in the art without improper hindsight.

The Hendrickson paper, the Everett paper and the Andrea paper also do not render obvious claims 1 and 7.

The Hendrickson paper relates to a system and process for expressing a recombinant selenomethionyl protein (thioredoxin) in *E.coli*. Selenomethionyl thioredoxins produced by the system and process were crystallized and characterized, and then analyzed through X-ray crystallography using a multiwavelength anomalous diffraction (MAD) phasing technique.

The Hendrickson paper does not describe or suggest, however, the benefit of maintaining a comprehensive database of sequence information for a plurality of proteins, and structural information and functional information for selected proteins. Moreover, the Hendrickson paper does not describe or suggest, for example, the following features of claim 1: (i) a database of

sequence information for a plurality of proteins, and structural information and functional information for selected proteins; (ii) at least one bioinformatics tool adapted to use the sequence information, structural information and functional information stored in the database to cluster the plurality of proteins into a plurality of families, in which, for each family, members of the family have corresponding homologous sequences; (iii) protein synthesis means for synthesizing for each family determined by the at least one bioinformatics tool a plurality of target proteins which are members of the family, using information stored in the database corresponding to the target proteins; and (iv) a homology model building tool adapted to use the refined model of the target protein retrieved from the database to develop a homology model of one or more predicted protein structures; and (v) the database is updated using the at least one bioinformatics tool and the developed homology model.

Similarly, the Hendrickson paper fails to describe or suggest at least the following features of claim 7: (a) systematically organizing sequence information for a plurality of proteins, and structural information and functional information for selected proteins into a database; (b) clustering the plurality of proteins into a plurality of families, in which, for each family, members of the family have corresponding homologous sequences, using at least one bioinformatics tool and the sequence information, structural information and functional information stored in the database; (c) synthesizing for each family determined in step (b) a plurality of target proteins which are members of the family, using information stored in the database corresponding to the plurality of target proteins; and (i) developing a homology model of one or more predicted protein structures using computational tools for homology model building

and the refined model of the target protein retrieved from the database, and updating the database by using the at least one bioinformatics tool and the developed homology model.

The Everett paper relates to a study to identify a gene (PDS) which is responsible for Pendred syndrome, a recessively inherited disorder with the hallmark features of deafness and thyroid goitre. The Pendred syndrome critical region was identified by using blood samples from a family of human subjects, many of whom suffered Pendred syndrome. GRAIL analysis of primary sequence data was performed to facilitate positional cloning of the PDS gene. It was predicted that PDS encodes a 780 amino acid protein (so-called "pendrin"). The pendrin amino acid sequence was used with the tools BLAST and PSI-BLAST to query a public sequence database, which yielded thirteen proteins with homologous sequences.

While the Everett paper appears to suggest linking an unknown protein to known proteins by identifying homologous sequences, the Everett paper does not describe or suggest, however, a system or method for determining experimentally **a plurality of three-dimensional atomic structures**, each of which is associated with a corresponding protein.

Moreover, the Everett paper, like the Hendrickson paper, does not describe or suggest, for example, the following features of claim 1: (i) a database of sequence information for a plurality of proteins, and **structural information** and functional information for selected proteins; (ii) at least one bioinformatics tool adapted to use the sequence information, **structural information** and functional information stored in the database to cluster the plurality of proteins into **a plurality of families**, in which, for

each family, members of the family have corresponding homologous sequences; (iii) protein synthesis means for synthesizing for each family determined by the at least one bioinformatics tool **a plurality of target proteins** which are members of the family, using information stored in the database corresponding to the target proteins; and (iv) a homology model building tool adapted to use the refined model of the target protein retrieved from the database to develop a **homology model of one or more predicted protein structures**; and (v) the **database is updated** using the at least one bioinformatics tool and the developed homology model.

Similarly, the Everett paper, like the Hendrickson paper, fails to describe or suggest at least the following features of claim 7: (a) systematically organizing sequence information for a plurality of proteins, and **structural information** and functional information for selected proteins into a database; (b) clustering the plurality of proteins into **a plurality of families**, in which, for each family, members of the family have corresponding homologous sequences, using at least one bioinformatics tool and the sequence information, **structural information** and functional information stored in the database; (c) synthesizing for each family determined in step (b) **a plurality of target proteins** which are members of the family, using information stored in the database corresponding to the plurality of target proteins; and (i) developing a **homology model of one or more predicted protein structures** using computational tools for homology model building and the refined model of the target protein retrieved from the database, and **updating the database** by using the at least one bioinformatics tool and the developed homology model.

The Andrea paper relates to using a neural network to predict

biological activity of chemical compounds. Specifically, a study of applications of neural networks in quantitative structure-activity relationships (QSARs) of dihydrofolate reductase inhibitors is discussed. The Andrea paper, like the Everett paper, does not describe or suggest, however, a system or method for determining experimentally a plurality of three-dimensional protein structures.

A combination of the teachings of the Hendrickson paper, the Everett paper and the Andrea paper still would not render unpatentable the claimed invention because neither the Hendrickson paper nor the Everett paper nor the Andrea paper describes or suggests, for example, a system for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, which comprises at least the following: (i) a database of sequence information for a plurality of proteins, and structural information and functional information for selected proteins; (ii) at least one bioinformatics tool adapted to use the sequence information, structural information and functional information stored in the database to cluster the plurality of proteins into a plurality of families, in which, for each family, members of the family have corresponding homologous sequences; (iii) protein synthesis means for synthesizing for each family determined by the at least one bioinformatics tool a plurality of target proteins which are members of the family, using information stored in the database corresponding to the target proteins; and (iv) a homology model building tool adapted to use the refined model of the target protein retrieved from the database to develop a homology model of one or more predicted protein structures; and (v) the database is updated using the at least one bioinformatics tool and the developed homology model.

Similarly, a combination of the teachings of the Hendrickson paper, the Everett paper and the Andrea paper does not render unpatentable the claimed invention set forth in claim 7 because neither the Hendrickson paper nor the Everett paper nor the Andrea paper describes or suggests a process for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, which comprises at least the following steps: (a) systematically organizing sequence information for a plurality of proteins, and structural information and functional information for selected proteins into a database; (b) clustering the plurality of proteins into a plurality of families, in which, for each family, members of the family have corresponding homologous sequences, using at least one bioinformatics tool and the sequence information, structural information and functional information stored in the database; (c) synthesizing for each family determined in step (b) a plurality of target proteins which are members of the family, using information stored in the database corresponding to the plurality of target proteins; and (i) developing a homology model of one or more predicted protein structures using computational tools for homology model building and the refined model of the target protein retrieved from the database, and updating the database by using the at least one bioinformatics tool and the developed homology model.

Should the Examiner disagree therewith, it is respectfully requested that the Examiner specify where in the cited document there is a basis for such disagreement.

Regarding claims 3, 5 and 6, applicants respectfully point out that claims 3, 5 and 6 depend on and include all the limitations

of claim 1. Thus, claims 3, 5 and 6 are patentable at least for the reasons set forth above with respect to claim 1.

Regarding claims 9, 11 and 12, applicants respectfully point out that claims 9, 11 and 12 depend on and include all the limitations of claim 7. Thus, claims 9, 11 and 12 are patentable at least for the reasons set forth above with respect to claim 7.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1, 3, 5-7, 9, 11 and 12 under 35 U.S.C. §103(a).

**Rejection Under 35 U.S.C. § 103(a)**

In Section 10 of the December 14, 2000 Office Action, claims 4 and 10 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the Bachar paper, the Hendrickson paper, the Everett paper and the Andrea paper, as applied to claims 1 and 7 above, and further in view of Lima et al. Structure 5, 763-774, 1997 (hereinafter "Lima paper").

The Examiner stated that claims 4 and 10 are drawn to the system and process of claims 1 and 7, respectively, wherein the synchroton storage ring has undulator beamlines for use with MAD.

The Examiner acknowledged that neither the Bachar paper nor the Hendrickson paper teaches a synchrotron storage ring which has undulator beamlines for use with MAD.

The Examiner stated that the Lima paper teaches using an undulator beamline X-ray source with MAD because of the high output levels, with narrow, tunable, harmonic peaks.

The Examiner alleged that it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the undulator beamline X-ray source, in place of the synchrotron device as taught by the Hendrickson paper, because a high output X-ray source, with narrow, tunable, harmonic peaks is disclosed in the Lima paper, and therefore, the invention as a whole purportedly would have been prima facie obvious at the time the invention was made.

Applicants maintain that the Bachar paper, the Hendrickson paper, the Everett paper, the Andrea paper and the Lima paper do not render unpatentable the invention set forth in claims 4 and 10. The claimed invention is patentable over the Bachar paper, the Hendrickson paper, the Everett paper, the Andrea paper and the Lima paper for at least the following reasons.

As stated above, the Bachar paper teaches away from, and therefore one skilled in the art would not have been motivated to combine the teachings of the Bachar paper with any teachings in the prior art of, a system for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, which comprises at least the following: (i) a database of **sequence information** for a plurality of proteins, and structural information and functional information for selected proteins; (ii) at least one bioinformatics tool adapted to use **the sequence information**, structural information and functional information stored in the database to cluster the plurality of proteins into a plurality of families, in which, for each family, members of the family have corresponding **homologous sequences**; and (iii) structure extraction means having means for analyzing the refined model of the target protein **using sequence information** corresponding to

other family members which is stored in the database and structural information corresponding to other proteins which is stored in the database, as set forth in thrice-amended claim 1, from which claim 4 depends.

Similarly, as stated above, the Bachar paper teaches away from, and therefore one skilled in the art would not have been motivated to combine the teachings of the Bachar paper with any teachings in the prior art of, a process for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, which comprises at least the following steps: (a) **systematically organizing sequence information** for a plurality of proteins, and structural information and functional information for selected proteins into a database, (b) clustering the plurality of proteins into a plurality of families, in which, for each family, members of the family have corresponding **homologous sequences**, using at least one bioinformatics tool and **the sequence information**, structural information and functional information stored in the database, and (h) analyzing the refined model, stored in the database, of the target protein **using sequence information** corresponding to other family members which is stored in the database and structural information corresponding to other proteins which is stored in the database, as set forth in thrice-amended claim 7, from which claim 10 depends.

As also stated above, the Hendrickson paper, the Everett paper and the Andrea paper fail to describe or suggest a system for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, which comprises at least the following:

(i) a database of sequence information for a plurality of proteins, and structural information and functional information for selected proteins; (ii) at least one bioinformatics tool adapted to use the sequence information, structural information and functional information stored in the database to cluster the plurality of proteins into a plurality of families, in which, for each family, members of the family have corresponding homologous sequences; (iii) protein synthesis means for synthesizing for each family determined by the at least one bioinformatics tool a plurality of target proteins which are members of the family, using information stored in the database corresponding to the target proteins; and (iv) a homology model building tool adapted to use the refined model of the target protein retrieved from the database to develop a homology model of one or more predicted protein structures; and (v) the database is updated using the at least one bioinformatics tool and the developed homology model, as set forth in thrice-amended claim 1, from which claim 4 depends.

Similarly, as stated above, the Hendrickson paper, the Everett paper and the Andrea paper also fail to describe or suggest a process for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, which comprises at least the following steps: (a) systematically organizing sequence information for a plurality of proteins, and structural information and functional information for selected proteins into a database; (b) clustering the plurality of proteins into a plurality of families, in which, for each family, members of the family have corresponding homologous sequences, using at least one bioinformatics tool and the sequence information, structural information and functional information stored in the database;

(c) synthesizing for each family determined in step (b) a plurality of target proteins which are members of the family, using information stored in the database corresponding to the plurality of target proteins; and (i) developing a homology model of one or more predicted protein structures using computational tools for homology model building and the refined model of the target protein retrieved from the database, and updating the database by using the at least one bioinformatics tool and the developed homology model, as set forth in thrice-amended claim 7, from which claim 10 depends.

The Lima paper describes a process using MAD analysis for determining the three-dimensional structure of fragile histidine triad (FHIT) protein. The Lima paper was cited in the Office Action for its description of use of an undulator beamline x-ray source with MAD.

The Lima paper, like the Bachar paper, the Hendrickson paper, the Everett paper and the Andrea paper, does not describe or suggest, however, a system for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, which comprises at least the following: (i) a database of sequence information for a plurality of proteins, and structural information and functional information for selected proteins; (ii) at least one bioinformatics tool adapted to use the sequence information, structural information and functional information stored in the database to cluster the plurality of proteins into a plurality of families, in which, for each family, members of the family have corresponding homologous sequences; (iii) protein synthesis means for synthesizing for each family determined by the at least one bioinformatics tool a plurality of target proteins which are

members of the family, using information stored in the database corresponding to the target proteins; and (iv) a homology model building tool adapted to use the refined model of the target protein retrieved from the database to develop a homology model of one or more predicted protein structures; and (v) the database is updated using the at least one bioinformatics tool and the developed homology model, as set forth in thrice-amended claim 1, from which claim 4 depends.

The Lima paper, like the Bachar paper, the Hendrickson paper, the Everett paper and the Andrea paper, also fails to describe or suggest a process for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, which comprises at least the following steps: (a) systematically organizing sequence information for a plurality of proteins, and structural information and functional information for selected proteins into a database; (b) clustering the plurality of proteins into a plurality of families, in which, for each family, members of the family have corresponding homologous sequences, using at least one bioinformatics tool and the sequence information, structural information and functional information stored in the database; (c) synthesizing for each family determined in step (b) a plurality of target proteins which are members of the family, using information stored in the database corresponding to the plurality of target proteins; and (i) developing a homology model of one or more predicted protein structures using computational tools for homology model building and the refined model of the target protein retrieved from the database, and updating the database by using the at least one bioinformatics tool and the developed homology model, as set forth in thrice-amended claim 7, from which claim 10 depends.

Therefore, the Bachar paper, the Hendrickson paper, the Everett paper, the Andrea paper and the Lima paper, considered alone or in combination, fail to teach or render obvious all features of the claimed invention.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 4 and 10 under 35 U.S.C. §103(a).

**Rejection Under 35 U.S.C. § 103(a)**

In Section 11 of the December 14, 2000 Office Action, claims 2 and 8 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the Bachar paper, the Hendrickson paper, the Everett paper, and the Andrea paper, as applied to claims 1 and 7, and further in view of U.S. Patent No. 5,525,198 to Craig et al. (hereinafter "the Craig patent").

The Examiner stated that claims 2 and 8 are drawn to the system and process of claims 1 and 7, respectively, wherein a cryogenic freezing means is used to freeze the target protein crystal.

The Examiner acknowledged that neither the Bachar paper nor the Hendrickson paper discloses the use of crogenic freezing means to freeze the target protein crystal.

The Examiner stated that the Craig patent teaches the cryogenic freezing of target protein crystals as a means of increasing the crystal's stability during exposure to X-ray sources.

The Examiner alleged that it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize a means for the cryogenic cooling of the target protein

crystal, with the system/process of the Bachar paper, in view of the Hendrickson paper, as the Craig patent teaches that cryogenic cooling preserves crystals during X-ray sampling, and therefore the invention as a whole purportedly would have been prima facie obvious at the time the invention was made.

Applicants maintain that the Bachar paper, the Hendrickson paper, the Everett paper, the Andrea paper and the Craig patent do not render unpatentable the invention set forth in claims 2 and 8. The claimed invention is patentable over the Bachar paper, the Hendrickson paper, the Everett paper, the Andrea paper and the Craig patent for at least the following reasons.

As stated above, the Bachar paper teaches away from, and therefore one skilled in the art would not have been motivated to combine the teachings of the Bachar paper with any teachings in the prior art of, a system for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, which comprises at least the following: (i) a database of **sequence information** for a plurality of proteins, and structural information and functional information for selected proteins; (ii) at least one bioinformatics tool adapted to use **the sequence information**, structural information and functional information stored in the database to cluster the plurality of proteins into a plurality of families, in which, for each family, members of the family have corresponding **homologous sequences**; and (iii) structure extraction means having means for analyzing the refined model of the target protein **using sequence information** corresponding to other family members which is stored in the database and structural information corresponding to other proteins which is stored in the database, as set forth in thrice-amended claim 1,

from which claim 2 depends.

Similarly, as stated above, the Bachar paper teaches away from, and therefore one skilled in the art would not have been motivated to combine the teachings of the Bachar paper with any teachings in the prior art of, a process for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, which comprises at least the following steps: (a) **systematically organizing sequence information** for a plurality of proteins, and structural information and functional information for selected proteins into a database, (b) clustering the plurality of proteins into a plurality of families, in which, for each family, members of the family have corresponding **homologous sequences**, using at least one bioinformatics tool and **the sequence information**, structural information and functional information stored in the database, and (h) analyzing the refined model, stored in the database, of the target protein **using sequence information** corresponding to other family members which is stored in the database and structural information corresponding to other proteins which is stored in the database, as set forth in thrice-amended claim 7, from which claim 8 depends.

As also stated above, the Hendrickson paper, the Everett paper and the Andrea paper fail to describe or suggest a system for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, which comprises at least the following: (i) a database of sequence information for a plurality of proteins, and structural information and functional information for selected proteins; (ii) at least one bioinformatics tool

adapted to use the sequence information, structural information and functional information stored in the database to cluster the plurality of proteins into a plurality of families, in which, for each family, members of the family have corresponding homologous sequences; (iii) protein synthesis means for synthesizing for each family determined by the at least one bioinformatics tool a plurality of target proteins which are members of the family, using information stored in the database corresponding to the target proteins; and (iv) a homology model building tool adapted to use the refined model of the target protein retrieved from the database to develop a homology model of one or more predicted protein structures; and (v) the database is updated using the at least one bioinformatics tool and the developed homology model, as set forth in thrice-amended claim 1, from which claim 2 depends.

Similarly, as stated above, the Hendrickson paper, the Everett paper and the Andrea paper also fail to describe or suggest a process for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, which comprises at least the following steps: (a) systematically organizing sequence information for a plurality of proteins, and structural information and functional information for selected proteins into a database; (b) clustering the plurality of proteins into a plurality of families, in which, for each family, members of the family have corresponding homologous sequences, using at least one bioinformatics tool and the sequence information, structural information and functional information stored in the database; (c) synthesizing for each family determined in step (b) a plurality of target proteins which are members of the family, using information stored in the database corresponding to the

plurality of target proteins; and (i) developing a homology model of one or more predicted protein structures using computational tools for homology model building and the refined model of the target protein retrieved from the database, and updating the database by using the at least one bioinformatics tool and the developed homology model, as set forth in thrice-amended claim 7, from which claim 8 depends.

The Craig patent relates to determination of the 3-D structure of a molecule by forming an electrorheological crystalline mass of the molecule, obtaining an X-ray diffraction pattern of the electrorheological crystalline mass, and calculating the 3-D structure of the molecule using the X-ray diffraction pattern. The Craig patent was cited was cited in the Office Action for its description of cryogenic freezing of target protein crystals as a means of increasing the crystal's stability during exposure to x-ray sources.

The Craig patent, like the Hendrickson paper, the Everett paper and the Andrea paper, does not describe or suggest, however, a system for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, which comprises at least the following: (i) a database of sequence information for a plurality of proteins, and structural information and functional information for selected proteins; (ii) at least one bioinformatics tool adapted to use the sequence information, structural information and functional information stored in the database to cluster the plurality of proteins into a plurality of families, in which, for each family, members of the family have corresponding homologous sequences; (iii) protein synthesis means for synthesizing for each family determined by the at least one bioinformatics tool

a plurality of target proteins which are members of the family, using information stored in the database corresponding to the target proteins; and (iv) a homology model building tool adapted to use the refined model of the target protein retrieved from the database to develop a homology model of one or more predicted protein structures; and (v) the database is updated using the at least one bioinformatics tool and the developed homology model, as set forth in thrice-amended claim 1, from which claim 2 depends.

The Craig patent, like the Hendrickson paper, the Everett paper and the Andrea paper, also fails to describe or suggest a process for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, which comprises at least the following steps: (a) systematically organizing sequence information for a plurality of proteins, and structural information and functional information for selected proteins into a database; (b) clustering the plurality of proteins into a plurality of families, in which, for each family, members of the family have corresponding homologous sequences, using at least one bioinformatics tool and the sequence information, structural information and functional information stored in the database; (c) synthesizing for each family determined in step (b) a plurality of target proteins which are members of the family, using information stored in the database corresponding to the plurality of target proteins; and (i) developing a homology model of one or more predicted protein structures using computational tools for homology model building and the refined model of the target protein retrieved from the database, and updating the database by using the at least one bioinformatics tool and the developed homology model, as set forth in thrice-amended claim

7, from which claim 8 depends.

Therefore, the Bachar paper, the Hendrickson paper, the Everett paper, the Andrea paper and the Craig patent, considered alone or in combination, fail to teach or render obvious all features of the claimed invention.

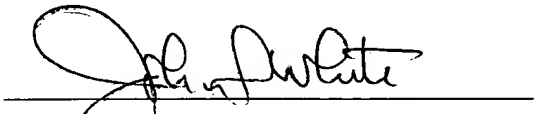
Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 2 and 8 under 35 U.S.C. §103(a).

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

If a petition for a further extension of time is required to make this response timely, this paper should be considered to be such a petition, and the Commissioner is authorized to charge the requisite fees to our Deposit Account No. 03-3125.

No fee, other than the fee for the one-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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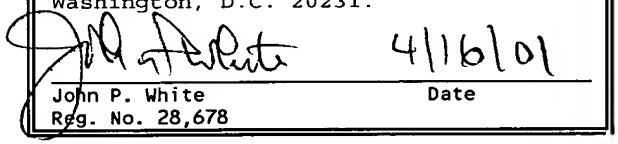

4/16/01

John P. White
Reg. No. 28,678

Date

C1

1. (Thrice Amended) A system for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, comprising:

SUB D1

a database of sequence information <u>for a plurality of proteins</u>, and [known] structural information and functional information [, which is systematically organized] for [a plurality of] <u>selected</u> proteins;

at least one bioinformatics tool [using] <u>adapted to use</u> the [structural information,] sequence information, <u>structural information</u> and functional information stored in the database to cluster the plurality of proteins into a plurality of families, in which, <u>for each family,</u> members of [each] <u>the</u> family have corresponding homologous sequences;

protein synthesis means for synthesizing for each family determined by the at least one bioinformatics tool a plurality of target proteins [, in parallel,] which are [appropriately representative] members of the family, using information stored in the database corresponding to the target proteins, the protein synthesis means having screening means for screening [the] products of the synthesis to [determine ones that are effective as proteins] <u>choose selected synthesized products for processing</u>;

protein processing means for preparing, purifying and characterizing each [target protein which is determined to be effective by the screening means] <u>of the selected synthesized products</u>;

crystallization means for crystallizing [each target protein] <u>the</u> processed [by the protein processing means] <u>synthesized product</u> against a plurality of crystallization screens [in parallel] to produce a plurality of specimen crystals of the target protein, and testing the plurality of specimen crystals for predetermined diffraction characteristics to

2. (Twice Amended) A system according to claim 1, further comprising:

cryoprotection means for freezing the suitable [ones of the plurality of] specimen crystals [of the target protein which are determined to be suitable by the crystallization means],

wherein the suitable specimen crystals [determined by the crystallization means to be suitable] are frozen by the cryoprotection means before being measured for diffraction data by the diffraction measuring means.

C1 concld

C2

6. (Twice Amended) A system according to claim 1, wherein the homology model developed by the homology model building tool is used in at least one of target selection, drug design, and design of [more appropriate] constructs for experimental analysis.

7. (Thrice Amended) A process for determining experimentally a plurality of three-dimensional atomic structures, each of which is associated with a corresponding protein, comprising the steps of:

Subj D2

(a) systematically organizing sequence information for a plurality of proteins, and [known] structural information and functional information [,] for [a plurality of] selected proteins into a database;

(b) clustering the plurality of proteins into a plurality of families, in which, for each family, members of [each] the family have corresponding homologous sequences, using at least one bioinformatics tool and the sequence information, structural information and functional information stored in the database;

(c) synthesizing for each family determined in step (b) a plurality of target proteins[, in parallel,] which are

C1 cont'd

determine suitable [ones of the plurality of] specimen crystals [of the target protein];

X-ray crystallography means for performing high-throughput crystallography on the specimen crystals of each target protein determined by the crystallization means to be suitable, the X-ray crystallography means having diffraction measuring means for measuring for diffraction data the suitable specimen crystals of the target protein, analyzing means for analyzing the diffraction data, means for building an atomic model of the target protein according to an analysis of the diffraction data by the analyzing means, and means for refining the model of the target protein against the diffraction data and storing the refined model in the database;

structure extraction means having means for analyzing the refined model of the target protein using sequence information corresponding to other family members which is stored in the database and structural information corresponding to other [known three-dimensional structures] proteins which is stored in the database, means for analyzing the refined model for functional motifs and for surface characteristics to define active sites and macromolecular contact sites, and means for defining at least one class of compounds predicted to have binding potency using the active sites information corresponding to the target protein; and

a homology model building tool [developing a homology model using] adapted to use the refined model of the target protein retrieved from the database to develop a homology model of one or more predicted protein structures,

wherein the database is updated using the at least one bioinformatics tool [along with] and the developed homology model.

C2 contd

[appropriately representative] members of the family, using information stored in the database corresponding to the plurality of target proteins, and screening products of the synthesis to [determine ones that are effective as proteins] choose selected synthesized products for processing;

(d) preparing, purifying and characterizing each [target protein which] synthesized product that is [determined to be effective] chosen in step (c);

(e) crystallizing [each target protein] the processed synthesized product prepared, purified and characterized in step (d) against a plurality of crystallization screens [in parallel] to produce a plurality of specimen crystals of the target protein;

(f) testing the plurality of specimen crystals [of one of the target proteins] grown in step (e) for predetermined diffraction characteristics to determine suitable [ones of the plurality of] specimen crystals of the [one] target protein;

(g) performing high-throughput crystallography, including measuring for diffraction data the specimen crystals [of the one target protein] determined in step (f) to be suitable, building an atomic model of the [one] target protein according to an analysis of the diffraction data, refining the model of the [one] target protein against the diffraction data, and storing the refined model in the database;

(h) analyzing the refined model, stored in the database in step (g), of the [one] target protein using sequence information corresponding to other family members which is stored in the database and structural information corresponding to other [known three-dimensional structures] proteins which is stored in the database, analyzing the refined model of the [one] target protein for functional motifs and for surface characteristics to define

active sites and macromolecular contact sites, and defining at least one class of compounds predicted to have binding potency using the active sites information corresponding to the [one] target protein;

(i) developing a homology model <u>of one or more predicted protein structures</u> using computational tools for homology model building and the refined model of the [one] target protein retrieved from the database, and updating the database by using the at least one bioinformatics tool [along with] <u>and</u> the developed homology model; and

(j) performing steps (f) through (i) for each of the other target proteins.

8. (Twice Amended) A process according to claim 7, further comprising the step of:

freezing the [suitable ones of the plurality of] specimen crystals of the [one] target protein which are determined in step (f) to be suitable,

wherein the [plurality of] <u>suitable</u> specimen crystals [determined to be suitable] are frozen before being measured for the diffraction data in step (g).

C2 cont'd

C3

12. (Twice Amended) A process according to claim 7, further comprising the step of

using the homology model developed in step (i) in at least one of target selection, drug design, and design of [more appropriate] constructs for experimental analysis.